UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,687	02/02/2001	Noel K. Maclaren	BII-001CP	3472

959 7590 06/03/2003

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	13

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,687	MACLAREN ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-18,20 and 33-44* is/are pending in the application.

4a) Of the above claim(s) *36-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,13-18,20,33 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

1. Claims 13-18, 20, 23, and 27 were pending, under consideration, and rejected in the prior action (mailed on September 10, 2002). As noted by Applicant, in the Response filed on March 17, 2003 (mailed on March 10, 2003) the Applicant cancelled claims 23, and 27 (along with other claims that were withdrawn from consideration as to non-elected inventions), amended claims 13-18, and 20, and added new claims 33-44. The amended and added claims comprise all of the currently pending claims. The pending claims are under examination to the extent that they read on methods of administering a bacterial cell lysate to a subject.

2. Newly submitted claims 36-41 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons: The newly submitted claims 36-41 are related as combination and subcombination with the originally elected invention. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). As the subcombination has the same utility as the newly added combinations, and as the combinations may rely on the additional limitations for patentability rather than the limitations of the subcombinations alone, the inventions of these sets of claims are distinct.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution

on the merits. Accordingly, claims 36-41 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

It is noted that USPTO linking claim practice applies among the elected invention and the newly withdrawn inventions.

3. The Examiner notes the Applicant's statement with regards to the traversal of the original restriction requirement. The election was made with traverse.

4. Because this action raises new issues not raised in the prior action, this action is being made Non-Final.

Specification

5. **(Prior Objection- Withdrawn)** The specification was objected in the prior action as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Claim 23 referred to a method of preventing an autoimmune disease by administrating an enhancing agent wherein the agent is a bacterial cell lysate. Although this claim has been cancelled, claims 13, 16, and 17 have been amended to incorporate this limitation. As the Applicant pointed out where support for this limitation may be found in the application, the objection is withdrawn.

Claim Objections

on the merits. Accordingly, claims 36-41 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

It is noted that USPTO linking claim practice applies among the elected invention and the newly withdrawn inventions.

3. The Examiner notes the Applicant's statement with regards to the traversal of the original restriction requirement. The election was made with traverse.

4. Because this action raises new issues not raised in the prior action, this action is being made Non-Final.

Specification

5. **(Prior Objection- Withdrawn)** The specification was objected in the prior action as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Claim 23 referred to a method of preventing an autoimmune disease by administrating an enhancing agent wherein the agent is a bacterial cell lysate. Although this claim has been cancelled, claims 13, 16, and 17 have been amended to incorporate this limitation. As the Applicant pointed out where support for this limitation may be found in the application, the objection is withdrawn.

Claim Objections

6. **(Prior Objection- Withdrawn)** Claim 16 was objected in the prior action to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter

of a previous claim. In view of the amendment to the claim, writing it in independent form, the objection is withdrawn.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. **(Prior Rejection- Reformed and Maintained)** Claim13-18, 20, 23, and 27 were rejected in the prior action under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using some enhancing agents to ameliorate or treat some autoimmune diseases, does not reasonably provide enablement for methods of using any bacterial enhancing agents to prevent any autoimmune disease. In view of the new enablement rejection regarding claim 13, and dependant claims 14, 15, 17-20, 33-35, and 42-45 below, the traversal of the claim rejection will be considered only to the extent that it relates to the therapies other than the prevention of the an autoimmune disease. The rejected claims have been amended such that they now read on methods of ameliorating the symptoms of an ongoing immune response to a self-antigen by administering an agent that activates NK-T or CD25+ cells, rather than to the ameliorations of the symptoms of an autoimmune disorder. Also, claims 23 and 27 have been cancelled, and claims 33-35, and 42-44 have been added. Therefore, the rejection is maintained as described below over claims 13-18, 20, 33-35, and 42-44. For the purposes of this rejection, the targeted disorders are referred to as autoimmune disorders or diseases.

The claims were rejected for lack of enablement for two reasons. First, that the applicant had not shown that every bacterial cell or substance would be effective in treating autoimmune diseases. Second, the Applicant had not shown that every autoimmune disease is susceptible to treatment by the bacterial compositions. It is assumed that amendments to the claims, specifying a specific characteristic of the disorders to be treated, were intended to satisfy the second part of the rejection. The Applicant also presented arguments in traversal of the rejection.

The Examiner is not persuaded by these arguments. However, in view of the following discussion, the rejection is reformed such that there is now a single basis of rejection. The Applicant has not shown that any bacterial lysate would be effective in the treatment of any autoimmune disease. Although some bacterial lysates may be effective in the treatment of one or more autoimmune diseases, in view of the discussion below, the Applicant has not enabled one skilled in the art to practice such methods without undue experimentation.

In the traversal, the Applicant argues that he Applicant has provided adequate guidance to those in the art such that further compositions usable in the claimed method, other than those identified in the application, may be easily identified through routine experimentation. The Applicant pointed to the examples of such enhancing agents of pages 14-18 of the application as examples of agents capable of activating NK-T and CD25+ cells, and argued that because the Applicant had disclosed method by which further enhancing agents may be identified, the Applicant has enabled those skilled in the art to practice the invention without undue experimentation. In short, the Applicant is arguing that two of the Wands factors, the presence of examples, and the amount of guidance provided, favor a finding of enablement.

The examples provided, and referred to, by the Applicant, and the methods of identifying compounds that activate NK-T and CD25+ cells are noted. However, the claims, to the extent they are being considered, cover the amelioration of, or prevention of the development of, an immune response to a self antigen comprising administering to the subject any bacterial lysate. The pages referred to by the Applicant identify particular compounds derived from bacteria, but do not identify any bacterial lysates that may be used in the invention. While the Applicant may have identified a number of potential agents, they have not identified a common structure or other non-functional characteristic that would have guided those in the art to lysates with the ability to treat an autoimmune disease.

However, because some bacterial lysates are known in the art as adjuvants, had the ability to activate NK-T or CD25+ cells been the only prerequisite to efficacy in the claimed method, the Applicant may have been enabled for the claims. Such is not the case. On pages 1-2 of the application, there is a discussion of the difference between the relationship of Th1 and Th2 immune pathways with autoimmune disorders. On page 2, lines 5-7, the specification states that at least with regards to IMD, an autoimmune diabetes, "while anti-islet Th1 responses are generally thought to be destructive, anti-islet Th2 responses are thought to be protective, acting to counter the Th1 responses that mediate IMD." The teachings by the Applicant indicate that it is not the activation of T-cells generally that is needed in the claimed method, but the ability to direct the activation towards the Th2 pathway. Thus, in order to be enabled for the claimed method, the Applicant must show that bacterial lysates in general are capable of so directing the subject immune responses.

The Applicant has not provided any evidence that bacterial lysates are capable of such direction, or provided any specific examples of bacterial lysates that are effective in the treatment of autoimmune disorders. The two examples of an effective therapy presented in the application are not bacterial lysates, but vaccines comprising specific components of specific pathogens. See e.g., CancerWEB Online Medical Dictionary, "diptheria-tetanus-pertussis vaccine," pneumococcal vaccine," and "pertussis vaccine." Thus, the Applicant has not, as they argued, provided examples of enhancing agents that fall within the scope of the present claims.

Although a dearth of such examples alone does not show a lack of enablement, other teachings in the art, in combination with the teachings in the application, would tend to indicate that certain bacterial lysates would not be effective. As described above, the specification indicates that the enhancing agents effective in treating autoimmune diseases should be capable of directing a body's immune response along the Th2 pathway. However, an article describing the effective adjuvant components of the Mycobacterial cell teaches that these components would not have that effect. Scanga et al., Drugs 59(6): 1217-21. Rather, the article states that the components of this bacteria has the ability to induce the Th1 immune response (page 1218); a response taught by the present application to be destructive in autoimmune diseases.

Furthermore, even if the Applicant had presented evidence that lysates of one or more bacteria would be effective at inducing the correct immune response, this would not have enabled those in the art to use the claimed method using any bacterial lysate. This is because the art teaches that similar fractions from different species of the same genus of bacteria can lead to opposite immune reactions. See, e.g. Stanford et al., WO 85/05034. Stanford demonstrates that a bacterial fraction from M. tuberculosis can induce autoimmune arthritis, while M vaccae can

protect the subject against it. Pages 5-6. Thus, there is a demonstration in the art of unpredictability in that bacterial cell fractions from related bacterial species can have opposite effects on the same organism.

In traversal of the obviousness rejections, the Applicant himself pointed out this unpredictability in the art. The Applicant recognized that the art teaches "different components of *M. tuberculosis* result in very different immune responses." The Applicant then continued: "Given the different outcomes observed when different forms of antigen were administered, one of ordinary skill in the art would not have been motivated to modify the teachings of the art to arrive at the use of the bacterial lysates presently claimed." See, Response, page 15, and Vershoor, columns 25-28. The applicant is, in essence, arguing that because the various antigens present in the cell lysates would cause different reactions, those in the art would not have expected the lysates to work the same as specific isolated cellular components. In view of this, the Applicant would have to demonstrate that the lysates, which one of ordinary skill in the art would not have expected operate in the same manner as the individual components, would indeed be capable of inducing the correct immune responses.

The application does not provide any working examples of lysates that can treat autoimmune disorders. Nor does the application provide any other evidence that the lysates would be capable of activating the correct immune pathway. Further, as discussed above, the application itself provides information that would indicate, when combined with the teachings in the art, that the methods as currently claimed would not be operative (i.e. the teachings regarding the Th1 and Th2 pathways, and their opposing effects on the autoimmune disorder). Thus, as the application does not provide any guidance to identify bacterial lysates effective in stimulating a

Th2 immune response, and as the art and application each provide information tending to show that not all lysates would be so effective, the Applicant is not enabled for the presently claimed methods.

9. **(New Rejection)** Claims 13-15, 17-20, 33-35, and 42-45 are rejected under 35 U.S.C. 112, first paragraph, while being enabling for methods of delaying or inhibiting the onset of immune responses to a self antigen using certain bacterial lysates, does not reasonably provide enablement for methods of preventing the development of such disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. These claims read on the prevention of an immune response to a self-antigen by administering to a subject a bacterial cell lysate. The applicant is not enabled for the methods of these claims. In the specification, the applicant has provided one "example" entitled "Prevention of Diabetes in NOD Mice given Bacterial Adjuvants." App., page 26, Example 4. However, this example only shows that mice injected with a DTP or pneumococcal vaccine had a lower incidence of diabetes than did control mice at given times after inoculation. However, there are two problems with these showings which tend to indicate that the applicant is not enabled for the claimed method of prevention

First, neither of these vaccines comprises a bacterial lysate as is presently claimed and under examination. The DPT vaccine is a subunit vaccine comprising multiple antigens from several bacterial species. See, CancerWEB Online Medical Dictionary, "diptheria-tetanus-pertussis vaccine," pneumococcal vaccine," and "pertussis vaccine." As neither the DPT or

pneumococcal vaccines comprise bacterial lysates themselves, but comprise specific bacterial antigens, or whole killed cells, they do not demonstrate the efficacy of the composition used in the claimed methods. Secondly, as stated above, the showing by the applicant only demonstrates a delay in the onset of diabetes. The results presented in Figure 4 or the application do not show that the vaccine compositions are effective in the prevention of the diabetes, only that they may be able to delay it. For these two reasons, the applicant is not enabled for the method of prevention claimed in claim 13, or its dependant claims.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. **(Prior Rejection-Withdrawn)** Claims 13-18, 20, and 23 were rejected in the prior action under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Number 5,830,475, issued to Aldovini et al. (Aldovini) and by published PCT application WO 85/05034, naming Stanford et al. as inventors. Prior to amendment in the Response, the rejected claims describe methods of preventing or ameliorating autoimmune diseases by administering to a subject an enhancing agent wherein the agent is a bacterium or a substance derived therefrom. The claims have now

been limited to methods wherein the substance derived from bacteria is a bacterial cell lysate. The Applicant traverses the rejection on the grounds that, although the references teach the use of bacterial cell fractions, they do not teach the use of complete bacterial lysates, defined by the Applicant as comprising, in addition to the cell wall, "all the other components of lysed bacterial cells." Response, page 12, in traversal of the rejection over Qin et al. In view of the claims amendments, and the distinction between fractions and lysates as stated by the applicant, the rejection is withdrawn.

12. **(Prior Rejection- Withdrawn)** Claims 13, 14, 16, 20, 21, and 27 were rejected in the prior action under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 6,350,457, issued to Watson et al. (Watson). In view of the claim amendments and the traversal in the Response, the rejection is withdrawn.

13. **(Prior Rejection-Withdrawn)** Claims 13, 14, 16, 17, 20, and 23 were rejected in the prior action under 35 U.S.C. 102(b) as being anticipated by Qin et al., J. Immunology 150:2072-2080 (Qin). These claims describe methods of preventing or treating autoimmune diseases by administering to a subject a bacterium or bacterial lysate. The Applicant traverses this rejection stating that the reference teaches the use of Freund's complete adjuvant, and arguing that this adjuvant comprises only of the mycobacterial cell wall. This traversal is not found persuasive as Freunds incomplete adjuvant comprises only the bacterial cell wall, while the complete adjuvant comprises the entire bacterium. See,

14. **(Prior Rejection-Withdrawn)** Claims 13-18, 20, and 27 were rejected in the prior action under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 6,361776 issued to Alain Delcayre (Delcayre). The rejection is withdrawn in view of the amendment of the claims, and the Applicant's arguments in traversal.

15. **(New Rejection)** Claims 13, 15, 17, 18, 34, 35, 42, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Czinn et al., U.S. Patent 5,538,729. This patent teaches a method of inducing an immune response in a person through the administration of a bacterial lysate. Claim 1. In view of the fact that the application teaches the administration of the same composition to the same population, the method would inherently achieve the same results. The reference therefore anticipates the identified claims.

16. **(New Rejection)** Claims 13, 15, 17, 18, 33, 34, 35, 42, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Monti, EP 0269928. These claims read on a method of administering a bacterial lysate to an open population of subjects. Monti teaches a number of bacterial lysates useful as vaccines. Because it teaches the compositions as vaccines, it inherently teaches the administration of such vaccines, and therefore the claimed method. Although the reference does not teach that the administration is effective in the prevention or inhibition of autoimmune disease development, because the method taught is identical to that of the rejected claims, it would also have inherently performed the same function.

17. **(New Rejection)** Claims 13, 15, 17, 34, 35, 42, and 44 are rejected under 35 U.S.C. 102(e) as being anticipated by Fattom et al., U.S. Patent 6,294,177. The claims have been described above. The reference teaches a method of administering a bacterial lysate to a person to induce an immune response. Because the rejected claims share the same method of administering the same composition to the same population, the reference anticipates the claims. As the reference describes the same method as the rejected claims, the disclosed method would inherently have had the same result as would be achieved by the method of the rejected claims.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. **(Prior Rejection- Withdrawn)** Claims 13-18, 20, 23, and 27 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Number 6,433,013 issued to Verschoor et al. (Verschoor), in view of Aldovini; and further in view of Watson and Qin. The rejection is withdrawn in view of the applicant's traversal, which was persuasive.

20. **(New Rejection)** Claims 13-15, 17, 18, 33, 34, 35, 42, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Salk et al., U.S. 6,017,543. The claims

have been described above. Salk et al. teaches anti-viral vaccines also comprising an adjuvant. See, claim 2, and column 8, lines 51-62. Among the adjuvants suggested by the application are bacterial lysates, including lysates of the bacteria Streptococcus. Thus, the reference teaches the administration of compositions comprising a bacterial lysate enhancing agent. Because the reference teaches the administration of compositions comprising bacterial lysates, and because such an administration would inherently have the same result as the claimed method, the patent renders the claimed invention obvious.

It is noted that the reference does not teach, or even mention the intended function of the claimed method. However, as the reference teaches the claimed method, the applicant's claim would be considered a recognition by the Applicant of an additional advantage of the invention described in the patent. Such advantages, where they "flow naturally from following the suggestion of the prior art cannot be the basis for patentability. " See, MPEP § 2145 II (quoting Ex Parte Obiaya, 227 U.S.P.Q. 58, at 60 (BPAI 1985). Thus, because the reference teaches the composition used in the present claims, and inherently suggests the claimed method (one would have known that the vaccine was for administration), the reference renders the identified claims obvious.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
May 23, 2003

James C. Housel
JAMES HOUSEL 6/1/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600